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A twin study of perfume-related respiratory symptoms

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Abstract

Respiratory symptoms from environmental perfume exposure are main complaints in patients with multiple chemical sensitivities and often coincide with asthma and or eczema. In this population-based twin study we estimate the heritability of respiratory symptoms related to perfume and if co-occurrences of the symptoms in asthma, atopic dermatitis, hand eczema or contact allergy are influenced by environmental or genetic factors common with these diseases. In total 4,128 twin individuals (82%) responded to a questionnaire. The heritability of respiratory symptoms related to perfume is 0.35, 95%CI 0.14-0.54. Significant associations ($p<0.05$) between perfume-related respiratory symptoms and asthma, atopic dermatitis, hand eczema or contact allergy are not attributable to shared genetic or shared environmental/familial factors, except possibly for atopic dermatitis where genetic pleiotropy with respiratory symptoms to perfume is suggested by an estimated genetic correlation of 0.39, 95%CI 0.09-0.72.

Keywords: Twin study; Multiple chemical sensitivity; Asthma; Atopic dermatitis; Hand eczema; Perfume; Respiratory symptoms

Introduction

Environmental perfume exposure may cause respiratory symptoms such as discomfort, breathing problems or cough (Berg et al., 2008; Elberling et al., 2005a, 2006). The symptoms are mostly mild, but can be severe and affect daily life activities (Berg et al., 2008; Elberling et al., 2005a; Labarge and McCaffrey, 2000).

The pathophysiology of perfume-related respiratory symptoms is unclear; but IgE-mediated allergy is unlikely (Elberling et al., 2005a, 2007). The symptoms are positively associated with asthma (Opiekun et al., 2003; Elberling et al., 2005a), as well as hand eczema (HE) and/or contact allergy (CA), independent of asthma, skin prick test reactivity to common aeroallergens, sex and psychological vulnerability (Elberling et al., 2004). Perfume-related respiratory symptoms are also a main complain in individuals with multiple chemical sensitivity (MCS) (Labarge and McCaffrey, 2000), a complex disorder with unknown etiology (Winder, 2002).

Possible explanations for the co-occurrence of perfume-related respiratory symptoms in HE, CA or asthma

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include 1) genetic factors 2) environmental factors 3) physiological factors associated with inflammation 4) increased general tendency to report symptoms.

In the attempt to elucidate the influence of genetic factors on respiratory symptoms it is relevant to include atopic dermatitis (AD), as AD influences both the development of asthma and HE (Dold et al., 1992; Meding and Swanbeck, 1989). Atopic dermatitis is a chronic skin conditions characterized by dry skin, inflammation and itch, and it is important to note that AD does not imply an IgE-antibody associated reaction. The development of AD is strongly influenced by mutations in the gene encoding the skin barrier protein filaggrin (Sandilands et al., 2007), and probably also influenced by several other genes (Morar et al., 2006). The development of asthma and HE are also influenced by genetic factors independent of AD (Los et al., 2001; Bryld et al., 2003), and it is uncertain to what extent genetic factors influence the development of contact allergies (Brasch et al., 2006).

Comparison of casewise concordances in monozygotic (MZ) and dizygotic (DZ) twins can be used to distinguish genetic from environmental causes of a certain phenotype (Martin et al., 1997), e.g. perfume-related respiratory symptoms. Polygenic modeling of quantitative genetics can be used to estimate the relative contribution of genetic and environmental factors to the observed data, by finding the model that best balances parsimony and goodness of fit with as few parameters as possible. Additionally, a co-twin control design is suitable to control for shared genetic and environmental factors, sex and age when associations between a phenotype and disease are investigated, in this case respiratory symptoms and inflammatory diseases in skin and airways (HE, AD, CA and asthma). Further, probandwise concordance rate analysis, i.e. comparisons between MZ and DZ pairs of combined categories of perfume-related respiratory symptoms and a disease conditional on the co-twin status may verify and detail if genetics are shared between the symptoms related to perfume and the diseases in question. Lastly, polygenic modeling allows investigating possible pleiotropy between traits, i.e. the effects of the same gene or set of genes on two different phenotypes.

We aimed to estimate the heritability of respiratory symptoms related to perfume and to investigate if perfume-related respiratory symptoms are influenced by genetic factors shared with asthma, HE, AD or CA.

Materials and methods

Study population

In 2005 a questionnaire focusing on diseases and symptoms in skin and airways was posted to 5048 twin individuals. The twins had previously participated in a population-based questionnaire survey in 1996 and were randomly selected for that study (Bryld et al., 2000). All twins were born between 1953 and 1976 and were living on Zealand or neighboring Danish islands in 1996. Zygosity had been determined in a previous questionnaire study and was based on the similarity method (Kyvik et al., 1995). This method gives a reliable diagnosis of zygosity in more than 95% of all twin pairs (Christiansen et al., 2003). The cohort of twins comprised same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs, a few triplets and quadruplets, and a minor group with unknown zygosity.

Questionnaire and definitions

The questionnaire included one question on self-reported perfume-related respiratory symptoms and one question on pollen-related respiratory symptoms used as reference in the statistical analysis. The questions were formulated in Danish and the questions in English reported here have not undergone any linguistic or cultural validation. Respiratory symptoms were defined in the questionnaire ahead of the two questions as an annoying experience, for example itching; sneezing, stinging, coughing or difficult in breathing. Then respondents were asked: ''Have you within the last 12 months experienced symptoms from your eyes, nose, mouth, throat or lungs elicited by other people's wearing of perfume, aftershave or deodorant''? Yes/ No, and ''Have you within the last 12 months experienced symptoms from your eyes, nose, mouth, throat or lungs elicited by pollen from grass or trees''? Yes/No.

A history of hand eczema was determined by two validated questions from The Nordic Occupational Skin Questionnaire (NOSQ-2002) (Susitaival et al., 2003; Svensson et al., 2002), phrased: ''Have you ever had hand eczema?'' and the 1-year prevalence was estimated by asking about the time of last eruption? Atopic dermatitis was defined by questions from the UK working party criteria (Williams et al., 1994) as a history of an itchy skin condition plus a minimum 2 of 4 minor criteria: 1) a history of flexural involvement 2) a history of generalized dry skin 3) onset of rash under the age of 2 years 4) a history of asthma/ allergic-rhinitis. Contact allergy was defined as at least one self-reported positive patch test to nickel, preservatives, perfume, rubber, plants, chromate or other. Asthma and allergic rhinitis was determined by an affirmative answer to the questions, ''Have you ever been told by a doctor that you have asthma?'' and ''Have you ever been told by a doctor that you have allergic rhinitis?'' respectively. Included in the questionnaire were also questions on smoking habits.

Statistics

SPSS version 14.0 and Stata 9 (Stata Corp) were used for data management, descriptive statistics, casewise concordances and multiple regression analyses (all twin individuals). Twin similarity on self-reported perfume-related respiratory symptoms was assessed by casewise concordances (the conditional probability of affected twin given that the co-twin is affected (Kyvik, 1997). Higher MZ concordance than DZ concordance suggests genetic influence under equal environments assumption of MZ and DZ twins. To investigate dependencies of the various diseases (HE, AD, CA and asthma), multiple logistic regression analysis including all twin individuals was conducted. Confidence intervals were corrected for intra-twin correlation using the option "cluster" in Stata. Self-reported perfume- and pollen-related respiratory symptoms, respectively, were dependent variables in these analyses, and HE, AD, CA and asthma were explanatory variables in the models. Further adjustments were made for sex, year of birth, allergic rhinitis and smoking status. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

To assess mutual genetic influence on the listed traits, twin pairs discordant for perfume-related respiratory symptoms (i.e. only one twin in a pair had perfume-related respiratory symptoms) were selected for co-twin control analysis estimating the risks of HE, AD, CA or asthma conditional on the status in the co-twin without respiratory symptoms, using Stata Statistical Software. The positive trend of more respiratory symptoms with increasing number of positive patch tests was investigated by logistic regression analysis.

To investigate if genes are shared between the symptoms related to perfume and the diseases in question, probandwise concordances (with 95% CIs) were calculated including all twin pairs (Mx statistical software, Neale et al. Virginia University, USA). We estimated the risks for MZ and DZ pairs of falling into a combined category of perfume-related respiratory symptoms and HE, AD, CA or asthma conditional on the co-twin status. To further quantify the genetic and environmental influences on respiratory symptoms (and AD selected according to the mutual concordance rate analysis above) biometric models were applied. The multivariate (continuous) liabilities to perfume-related respiratory symptoms and selected traits were decomposed into an additive genetic component, A, a dominant genetic component, D, a shared environmental component, C, and an environmental component, E, accounting for individual environmental effects. The polygenic model of quantitative genetics (Falconer, 1960) allows for estimating up to three of these components simultaneously assuming that MZ twins in a pair share all their genetic material, while DZ pairs on average share half their genetic material, as do siblings in general. Heritability of perfume-related respiratory symptoms was then estimated under the best fitting sub-model among models of same type for each trait in a sense of likelihood comparison and the principle of parsimony summarized in the Akaike index criterion (AIC). This model further allows estimation of correlation between traits at genetic and environmental level and hence, in particular, provides information on the presence of genetic pleiotropy between respiratory symptoms and AD.

Results

The response rate to the questionnaire was 82% (4,128/5,048) and the responders comprised 1,717 MZ twin individuals, 2,198 DZ twin individuals, 44 triplet individuals, two quadruplets, and 167 individuals with unknown zygosity. Because 577 and 564 individuals responded as the only member in MZ and DZ twin pairs respectively, only 570 MZ pairs and 817 DZ pairs were available for concordance analysis. Females accounted for 59.0% of the responders and the mean age of the twin individuals was 40.4 years (SD 6.6, range 28–52). Characteristics of respondents and non-respondents have been described previously (Lerbaek et al., 2007). The overall prevalence of perfume-related respiratory symptoms was 8% and was similar in MZ and DZ pairs (Table 1). The occurrence of symptoms was significantly ($p<0.05$) increased in the total population when a co-twin was also affected by symptoms. The higher concordance in female MZ twins (0.25) as compared with female DZ twins (0.13) suggests an influence of genetic factors on perfume-related respiratory symptoms (Table 1). In multiple logistic regression analysis, significant associations between perfume-related respiratory symptoms and asthma, HE, CA, and AD were found independent of allergic rhinitis, present smoking, sex and year of birth (Table 2). The occurrence of symptoms was significantly ($p<0.05$) influenced by sex and year of birth with trends going in opposite directions depending on whether symptoms were reported from perfume or pollen (Table 2). An extreme positive and significant (expected) association (OR 42.3) was found between respiratory symptoms related to pollen and allergic rhinitis. Further, the symptoms from pollen were positively associated with asthma, whereas they were not associated with HE, AD or CA (Table 2). Perfume-related respiratory symptoms increased significantly with the number of self-reported positive patch tests (Fig. 1), which was not the case for pollen-related respiratory symptoms.

In total 176 twin pairs were discordant for perfume-related respiratory symptoms; Table 3 shows the results from conditional analysis in the 69 MZ and 107 DZ

Table 1. Casewise concordance of perfume-related respiratory symptoms occurring in the previous 12 months.

	Eye or respiratory symptoms related to perfume in the previous12 months						
	pairs	cases#	concordant pairs	discordant pairs	prevalence	casewise concordance (95%CI)	p-value
Females	817	159	14	131	0.10	0.18 (0.10-0.27)	
Males	570	51	3	45	0.04	0.12 (0.03-0.29)	
ALL	1387	210	17	176	0.08	0.16 (0.09-0.23)	
MZF	362	63	8	47	0.09	0.25 (0.11-0.40)	
DZF	455	96	6	84	0.10	0.13 (0.03-0.22)	0.077*
MZM	270	26	2	22	0.05	0.15 (0.03-0.34)	
DZM	300	25	1	23	0.04	0.12 (0.07-0.23)	0.27*

MZF: Monozygotic female; DZF: Dizygotic female; MZM: Monozygotic male; DZM: Dizygotic male.
Number of individuals (within pairs) with self-reported perfume-related respiratory symptoms in the previous 12 months.
*P-value comparing casewise concordance between MZ and DZ twins.

Table 2. Logistic regression models with perfume- or pollen-related respiratory symptoms as dependent variables and hand eczema, positive path tests, atopic dermatitis and asthma as explanatory variables.

	Respiratory symptoms related to			
	Other people's wearing of perfume		Pollen from grass or trees	
	OR	95%CI[1]	OR	95%CI[1]
Hand eczema[2]	**1.62**	**1.17-2.24**	1.02	0.72-1.44
Contact allergy[3]	**1.54**	**1.10-2.17**	0.73	0.49-1.09
Atopic dermatitis[4]	**2.00**	**1.45-2.76**	1.34	0.99-1.82
Doctor diagnosed asthma	**2.34**	**1.68-3.25**	**1.43**	**1.01-2.05**
Doctor diagnosed allergic rhinitis	1.27	0.93-1.73	**42.3**	**33.1-54.2**
Current smoking	0.91	0.71-1.18	1.01	0.85-1.18
Female sex	**1.78**	**1.34-2.36**	0.94	0.76-1.19
Year of birth[5]				
1969-76	**1; $p<0.05$**		1; $p = 0.06$	
1961-68	**1.92**	**1.35-2.74**	0.95	0.74-1.22
1953-60	**2.27**	**1.60-3.24**	**0.72**	**0.55-0.96**

[1]odds ratio and 95% confidence intervals were adjusted for clusters in pairs plus the other explanatory variables. Significant associations are shown in bold.
[2]in the previous12 months.
[3]at least one positive patch tests to nickel, preservatives, perfume, rubber, plants, chromate or other.
[4]UK working party criteria (Williams et al., 1994).
[5]p-value for test for trend.

discordant twin pairs. HE was significantly associated with respiratory symptoms in both MZ and DZ pairs discordant for perfume-related respiratory symptoms, whereas AD was significantly associated with symptoms in DZ twins and all twins. A positive association between asthma and perfume-related respiratory symptoms was significant only in the total group of twins. No association was found between CA and respiratory symptoms OR = 1.0, 95% CI 0.56-1.93 in pairs discordant for respiratory symptoms (Table 3).

The prevalence of the combined categories of respiratory symptoms within pairs was comparably the same in MZ and DZ twin pairs (the rightmost column in Table 4a-d). The concordance of each state is given along the diagonal in the MZ and DZ parts of each table. Concordance rates along the diagonals and along the off-diagonals were no greater for MZ twins than for DZ twins, except for the concordance rates of AD + PS-/AD + PS- (PS refers to perfume-related respiratory symptoms) being significantly greater in MZ than in DZ twins in Table 4c, where several estimates differed non-significantly in equivalent cells of MZ and DZ twins.

Biometrical modelling of liability to perfume-related respiratory symptoms showed that decomposition into additive genetic effects and non-shared environmental

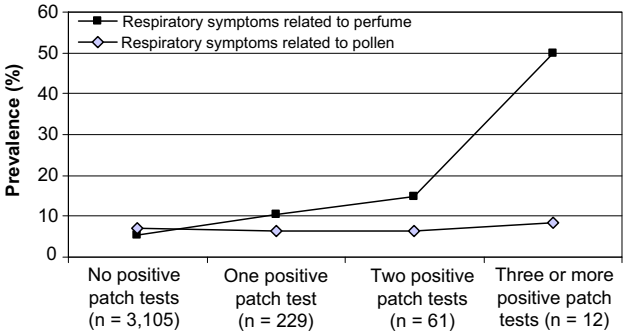

Fig. 1. P-value for test for trend <0.001 on perfume-related respiratory symptoms. Individuals with allergic rhinitis were excluded from the analysis.

Table 3. Case co-twin analysis including twin pairs discordant for perfume-related respiratory symptoms in the previous12 months.

	Pairs	OR	95%CI
Hand eczema[2]	176	**3.60**	**1.75-8.13**
MZ	69	**4.33**	**1.19-23.71**
DZ	103	**3.29**	**1.36-9.07**
Atopic dermatitis[3]	176	**2.33**	**1.31-4.31**
MZ	69	1.71	0.62-5.14
DZ	103	**2.72**	**1.33-6.03**
Doctor diagnosed asthma	176	**2.27**	**1.08-5.12**
MZ	69	2.25	0.63-10.0
DZ	103	2.29	0.89-6.57
Positive patch tests	176	1.04	0.56-1.93
MZ	69	0.54	0.17-1.61
DZ	103	1.50	0.68-3.41

Associations between the symptoms and hand eczema, atopic dermatitis, asthma or positive patch tests are shown in all pairs as well as in monozygotic (MZ) and dizygotic (DZ) twin pairs.
[1]odds ratio and 95% confidence intervals. Significant associations are shown in bold.
[2]in the previous 12 months.
[3]UK working party criteria (Williams et al., 1994).

factors gave best fit to observations and the heritability of perfume-related respiratory symptoms was estimated to 0.35, 95% CI 0.14-0.54. The best fitting polygenic model was the AE model which did not significantly deviate from the fit of the ADE and ACE models as shown in Table 5. Although the DE model showed a slightly better fit in terms of AIC it is not considered plausible for general traits (Eaves, 1988); the model fitting analysis for females and males was combined because variance components in the AE model did not differ significantly between sexes. However, thresholds (and hence prevalences) were allowed to depend on gender in each model (results not shown). The heritability of atopic dermatitis was 0.50, 95% CI 0.39-0.72 estimated by polygenic modelling; further, mutual genetic correlation of 0.39, 95%CI 0.09-0.72 was found between perfume-related respiratory symptoms and atopic dermatitis, indicating substantial genetic pleiotropy for these two traits.

Discussion

Perfume-related respiratory symptoms were reported twice as often by MZ than by DZ female twins if the co-twin had symptoms. This tendency was less distinct in male twins, suggesting either an overall limited influence of genetic factors on the phenotype or more complex gene-environment interactions underlying the symptoms. Accordingly, polygenic modeling suggests that only about one third of the phenotypic variation was due to additive genetic factors and the rest was attributable to environmental factors unique to the affected twin individual.

A question on respiratory symptoms related to pollen was included in the study in order to investigate if the association between perfume-related respiratory symptoms and the inflammatory conditions was caused by increased tendency to report symptoms. This was not indicated, because individuals with HE, CA and AD did not report pollen-related respiratory symptoms more often than other persons (Table 2 and Fig. 1).

The high odds ratio (42.3) on pollen-related respiratory symptoms and doctor diagnosed allergic rhinitis confirmed that to a high extent this phenotype is a clinical expression of IgE-mediated allergy, which is not the case for the perfume-related symptoms. Contrary to pollen-related respiratory symptoms, which appeared most frequently in the youngest age groups, perfume-related respiratory symptoms increased with age (Table 2) and were as previously found more frequent in females. This trend is opposite that of IgE-mediated allergy, which in Denmark is most common in individuals born after 1960 (Linneberg et al., 2007). The different prevalence estimate of respiratory symptoms between sexes could reflect gender-related environmental risk factors, e.g. increased exposure to scented

personal care products in females as compared with males, but other factors, e.g. differences in hormonal levels, should also be considered.

The significant associations found between the respiratory symptoms and each of the phenotypes (asthma, AD, HE and CA) were controlled for the possible effect of sex, age, and shared genetic and/ or environmental/ familial factors by co-twin control analysis (Table 3). The analyses suggest that the co-occurrence of respiratory symptoms with asthma, HE and AD was independent of shared genetic and/or environmental/ familial factors. The results from the probandwise concordance rate analyses agree with the above findings by confirming that the significant associations between respiratory symptoms and diseases could not be ascribed to effects of genes shared between the respiratory symptoms and the diseases, except for AD. The differences in the diagonals and off-diagonals between the MZ and DZ twins in Table 4c were probably due to pleiotropic genes between AD and respiratory symptoms, as also suggested by multivariate polygenic modelling. To our knowledge this is the first study to suggest that individuals with AD more frequently than others experience respiratory symptoms from perfume exposure independent of asthma. Further, we found that 39% of the association between perfume-related respiratory symptoms and AD was due to genetic components shared with AD. Future studies need to address to what extent mutations in filaggrin (Sandilands et al., 2007) or other candidate genes of AD (Morar et al., 2006) influence the occurrence of perfume-related respiratory symptoms.

Perfume-related respiratory symptoms increased significantly with the number of positive patch tests (Fig. 1). To a certain degree this replicates findings on respiratory symptoms related to airborne chemicals (other than perfumes) emerging with increasing number of positive patch tests in 1189 individuals patch tested with the European patch test series (Elberling et al., 2005b). Because the positive OR between respiratory symptoms and CA in Table 2 decreased to 1.0, 95%CI 0.56-1.93 in the co-twin control analysis (Table 3), shared genetic or familial environment of contact allergies might influence the development of perfume-related respiratory symptoms. However, the good accordance between MZ and DZ (in the diagonals and off-diagonals) (Table 4b) did not confirm that genes might be shared between the two traits.

Table 4. (a–d) Probandwise concordance rates and 95% confidence intervals expressing the risks for MZ and DZ pairs of falling into a combined category of perfume-related respiratory symptoms (PS) and hand eczema (HE), contact allergy (CA), atopic dermatitis (AD) or asthma (AS) conditional on the co-twin status.

(a)

MZ pairs	Co-twin				
Twin	HE+ PS+	HE+ PS-	HE-PS+	HE-PS-	Prevalence
HE+ PS+	0.00 (0.00;0.17)	0.01 (0.00;0.03)	0.09 (0.04;0.17)	0.01 (0.00;0.02)	0.02 (0.01;0.02)
HE+ PS-	0.05 (0.00;0.20)	0.21 (0.12;0.31)	0.04 (0.01;0.11)	0.09 (0.07;0.11)	0.10 (0.08;0.12)
HE- PS+	0.30 (0.13;0.52)	0.02 (0.01;0.06)	0.12 (0.06;0.24)	0.05 (0.04;0.06)	0.05 (0.04;0.07)
HE- PS-	0.65 (0.43;0.83)	0.76 (0.66;0.85)	0.75 (0.62;0.85)	0.85 (0.82;0.87)	0.83 (0.81;0.85)
DZ pairs					
HE+ PS+	0.00 (0.00;0.13)	0.02 (0.01;0.05)	0.01 (0.00;0.05)	0.02 (0.00;0.03)	0.02 (0.01;0.03)
HE+ PS-	0.11 (0.03;0.26)	0.14 (0.08;0.23)	0.07 (0.03;0.14)	0.10 (0.08;0.12)	0.10 (0.09;0.12)
HE- PS+	0.04 (0.00;0.15)	0.05 (0.02;0.09)	0.13 (0.05;0.24)	0.06 (0.05;0.07)	0.06 (0.05;0.08)
HE- PS-	0.85 (0.68;0.95)	0.79 (0.71;0.86)	0.78 (0.68;0.88)	0.82 (0.80;0.84)	0.82 (0.80;0.84)

(b)

MZ pairs	Co-twin				
Twin	CA+ PS+	CA+ PS-	CA- PS+	CA- PS-	Prevalence
CA+ PS+	0.01 (0.01;0.28)	0.01 (0.00;0.04)	0.05 (0.02;0.12)	0.01 (0.00;0.01)	0.01 (0.01;0.02)
CA+ PS-	0.09 (0.01;0.34)	0.26 (0.16;0.38)	0.14 (0.07;0.24)	0.06 (0.05;0.08)	0.08 (0.07;0.10)
CA- PS+	0.36 (0.13;0.64)	0.10 (0.05;0.17)	0.15 (0.07;0.28)	0.05 (0.04;0.06)	0.06 (0.05;0.08)
CA- PS-	0.54 (0.26;0.80)	0.63 (0.52;0.73)	0.65 (0.53;0.77)	0.88 (0.86;0.90)	0.85 (0.82;0.87)
DZ pairs					
CA+ PS+	0.01 (0.00;0.13)	0.05 (0.02;0.09)	0.02 (0.00;0.06)	0.01 (0.01;0.02)	0.02 (0.01;0.03)
CA+ PS-	0.26 (0.12;0.44)	0.21(0.13;0.31)	0.13 (0.07;0.21)	0.08 (0.06;0.10)	0.09 (0.08;0.12)
CA- PS+	0.07 (0.01;0.21)	0.08 (0.04;0.13)	0.11 (0.04;0.21)	0.06 (0.04;0.08)	0.06 (0.05;0.08)
CA- PS-	0.66 (0.48;0.82)	0.66 (0.57;0.75)	0.74 (0.64;0.84)	0.85 (0.83;0.87)	0.82 (0.80;0.84)

Table 4 (*continued*)

(c)

MZ pairs	Co-twin				
Twin	AD+ PS+	AD+ PS-	AD- PS+	AD- PS-	Prevalence
AD+ PS+	0.22 (0.06;0.45)	0.04 (0.02;0.07)	0.03 (0.00;0.09)	0.01 (0.01;0.02)	0.02 (0.01;0.03)
AD+ PS-	0.26 (0.12;0.45)	0.38 (0.30;0.47)	0.14 (0.07;0.24)	0.11 (0.09;0.13)	0.15 (0.13;0.18)
AD- PS+	0.07 (0.01;0.22)	0.05 (0.02;0.08)	0.16 (0.06;0.30)	0.04 (0.03;0.06)	0.05 (0.04;0.06)
AD- PS-	0.44 (0.26;0.65)	0.54 (0.45;0.62)	0.67 (0.53;0.79)	0.83 (0.81;0.86)	0.78 (0.75;0.80)
DZ pairs					
AD+ PS+	0.09 (0.01;0.24)	0.05 (0.02;0.08)	0.04 (0.01;0.10)	0.03 (0.01;0.04)	0.03 (0.02;0.04)
AD+ PS-	0.20 (0.10;0.33)	0.19 (0.12;0.27)	0.12 (0.06;0.21)	0.12 (0.10;0.14)	0.13 (0.11;0.15)
AD- PS+	0.07 (0.02;0.16)	0.05 (0.02;0.08)	0.05 (0.01;0.16)	0.05 (0.04;0.06)	0.05 (0.04;0.06)
AD- PS-	0.65 (0.50;0.79)	0.72 (0.64;0.79)	0.78 (0.67;0.87)	0.81 (0.78;0.83)	0.79 (0.77;0.81)

(d)

MZ pairs	Co-twin				
Twin	AS+ PS+	AS+ PS-	AS- PS+	AS- PS-	Prevalence
AS+ PS+	0.09 (0.01;0.32)	0.07 (0.03;0.13)	0.06 (0.02;0.13)	0.01 (0.00;0.02)	0.02 (0.01;0.03)
AS+ PS-	0.32 (0.15;0.53)	0.35 (0.24;0.47)	0.06 (0.02;0.13)	0.05 (0.04;0.07)	0.08 (0.07;0.10)
AS- PS+	0.18 (0.06;0.38)	0.04 (0.01;0.09)	0.15 (0.06;0.28)	0.05 (0.03;0.06)	0.05 (0.04;0.07)
AS- PS-	0.41 (0.22;0.62)	0.54 (0.43-0.66)	0.73 (0.60;0.84)	0.90 (0.87;0.91)	0.85 (0.82;0.87)
DZ pairs					
AS+ PS+	0.08 (0.01;0.29)	0.04 (0.01;0.09)	0.03 (0.01;0.08)	0.01 (0.01;0.02)	0.02 (0.01;0.02)
AS+ PS-	0.16 (0.05;0.34)	0.14 (0.06;0.25)	0.07 (0.03;0.14)	0.06 (0.05;0.07)	0.07 (0.05;0.08)
AS- PS+	0.12 (0.03;0.28)	0.07 (0.03;0.13)	0.06 (0.02;0.15)	0.06 (0.05;0.08)	0.06 (0.05;0.08)
AS- PS-	0.64 (0.43;0.82)	0.75 (0.64;0.84)	0.83 (0.74;0.91)	0.87 (0.85;0.89)	0.85 (0.83;0.87)

HE; Hand eczema in the previous 12 months.
PS; Perfume-related respiratory symptoms.
Diagonals appear grey coloured.
CA; Contact allergy, i.e. self-reported positive patch test.
PS; Perfume-related respiratory symptoms.
Diagonals appear grey coloured.
AD; Atopic dermatitis, UK working party criteria (Williams et al., 1994).
PS; Perfume-related respiratory symptoms.
Diagonals appear grey coloured.
AS; Doctor diagnosed asthma.
PS; Perfume-related respiratory symptoms.
Diagonals appear grey coloured.

Table 5. Biometric polygenic modelling for the two traits perfume-related respiratory symptoms and atopic dermatitis.

Model	LH	ΔX^2	Δdf	P	AIC	a^2	d^2	c^2	e^2	GC
ADE/ADE	5339.375	-	-	-	-10298.625	0.06/0.20	0.33/0.32	-/-	0.61/0.48	1
ACE/ACE	5341.348	-	-	-	-10296.652	0.35/0.50	-/-		0.65/0.50	0.39
AE/AE	5341.348	1.973	3	0.578	-10302.652	0.35/0.50	-/-	-/-	0.65/0.50	0.39
DE-DE	5339.375	0.462	3	0.927	-10304.163	-/-	0.39/0.53	-/-	0.61/0.47	-
CE-CE	5354.570	13.22	3	0.004	-10289.430	-/-	-/-	0.22/0.36	0.78/0.64	-
E-E	5404.028	62.68	6	0.000	-10245.972	-/-	-/-	-/-	1.0/1.0	-

Model fit (AIC) and parameter estimates for fitted biometric polygenic models of same type for the two traits perfume-related respiratory symptoms and atopic dermatitis. Variances of components A, D, C and E are denoted a^2, d^2, c^2 and e^2, respectively.
LH: Log-Likelihood (-2ll); ΔX^2: Difference in chi^2; Δdf: Difference in degrees of freedom; P: p-value; AIC: Akaike index criterion; GC: Genetic correlation.

Hand eczema, CA, AD and asthma are diseases with more or less chronic inflammation. One possible explanation for the observed associations is that the intrinsic environment related to tissue inflammation in otherwise susceptible individuals increases the sensitivity to inhaled perfume chemicals. This could be due to mechanisms at a peripheral level, for example, those possibly involved in bronchial sensory hyperreactivity, suggested in patients with lower respiratory symptoms related to chemicals (Millqvist et al., 1998), or it could involve an abnormal central processing of sensory odour signals, as suggested in patients with multiple chemical sensitivities (Hillert et al., 2007; Yunus, 2008).

In conclusion, we found an increased familial occurrence of perfume-related respiratory symptoms where 35% of phenotypic variation was due to additive genetic effects and 65% was due to individual specific environmental effects. The co-occurrence of symptoms with HE, CA and asthma was not attributable to shared genetic factors or shared environment during childhood whereas about 40% of the correlation of symptoms with AD was attributable to genes shared between AD and the respiratory symptoms related to perfume.

Conflict of Interest: None

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